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SYNTHESIS OF CARBAPENEMS WITH CARBON SUBSTITUENTS AT C-3 USING A WITTIG APPROACH

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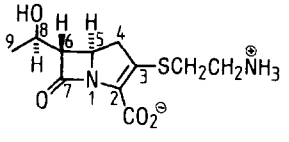
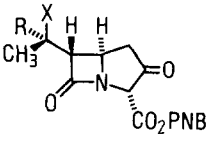
Summary: Reaction of ketone 2 with phosphorane 4 produced a mixture of endocyclic and exocyclic carbapenem esters 5 and 6. Hydrogenolysis of these gave carbapenems 7 and 8 or carbapenams 9 and 10.

Carbapenems are an important new class of antibiotics of which thienamycin (1) is the most well-known example[1]. They distinguish themselves from the classical ß-lactams such as penicillins and cephalosporins by their broad-spectrum antibacterial activity, covering a wide range of both gram-positive and gram-negative bacteria. One of the main obstacles on their way to useful therapeutic agents is their instability towards renal dehydropeptidase leading to low urinary recovery[2]. In an attempt to identify carbapenems with greater metabolic stability we have synthesized carbapenems with fluorine instead of hydroxyl in the 8-position[3]. In this communication we report our synthetic efforts towards syntheses of carbapenems that in addition are devoid of sulphur in the side chain at C-3. Published syntheses of C-3 carbon substituted carbapenems[4] have always relied on variations on the method originally developed by Woodward and coworkers[5].



1



2

a. R=H, X=OR (R=protectivegroup)
b. R=H, X=F
c. $R=CH_3$, X=F

We were intrigued by the possibility of using bicyclic ketone 2 as precursor for this class of carbapenems. This compound (i.e. 2a) was developed by Merck chemists as intermediate for the syntheses of sulphur substituted carbapenems[6]; in our laboratories we have used 2b and 2c for the same purpose[3]. The ketone moiety in 2 is exceptionally reactive for its kind: We found that most nucleophiles react instantaneously with 2b,c giving rise to ring-opened products of type 3 (Scheme 1)[7]. We were therefore gratified to find that stabilized phosphoranes 4 reacted with 2b,c to produce an inseparable mixture of 3-substituted carbapenem esters 5 (endo) and 6 (exo; E and Z)[8,9] (Scheme 2, for conditions and yields see Table 1).

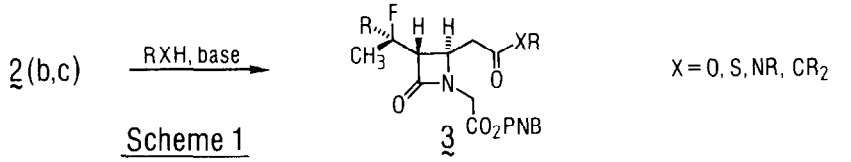
Table 1: Reaction of bicyclic ketone 2 with phosphoranes 4*

Entry	R	Z[11]	Conditions	Yield**	Product Ratio[10] 5	6-E	6-Z	Suffix
1	CH_3	CN	CH_2Cl_2, RT, 20 hrs.	68 %	51	36	13	k
2	CH_3	CO_2Et	CH_2Cl_2, RT, 2 hrs.	94 %	83	12	5	l
3	H	CN	CH_2Cl_2, RT, 2.5 hrs.	82 %	56	34	9	m
4	H	CO_2Et	CH_2Cl_2, RT, 0.75 hrs.	83 %	93	5	2	n
5	H	$COCH_3$	CH_2Cl_2, reflux 5 hrs.	43 %	38	62	--	o

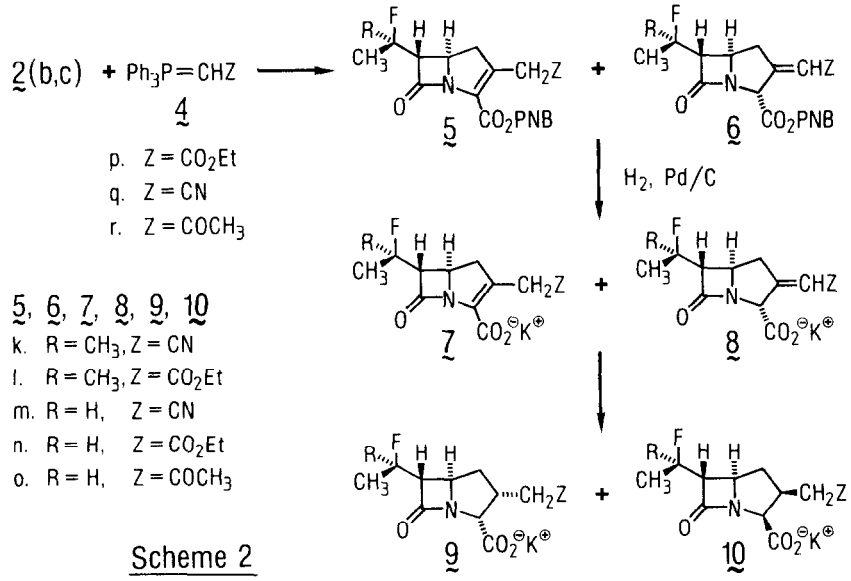
* 1.5 eq of phosphorane, c = 0.05 - 0.07 mol/l

** Yields of purified products (column chromatography: silica, CH_2Cl_2).

With phosphoranes 4p and 4q the reaction proceeded very smoothly at room temperature. Reaction between 2b and 4r was more sluggish and took 5 hrs. at CH_2Cl_2 reflux temperature. Reactions with more basic phosphoranes such as $Ph_3P{=}CHCl$[12] and $Ph_3P{=}CHSCH_3$[13] did not lead to products and bicyclic ketone 2 was recovered in good yield; presumably hydrogen exchange occurred.



Scheme 1



Scheme 2

Unfortunately, hydrogenolytic removal of the p-nitrobenzyl protective ester caused serious problems. Only with the cyanomethyl substituted carbapenem esters (5,6k and 5,6m) were we able to obtain carbapenem potassium salts 7 and 8 as inseparable mixtures in moderate yields, when short hydrogenation times were used (Table 2).

Table 2: Hydrogenolysis of carbapenem p-nitrobenzyl esters (5,6)*

Entry	R	Z	Time	Yield	Product Ratio					Suffix
					7	8E	8Z	9	10	
1	CH_3	CN	1 hr.	43 %	35	53	12	traces		k
2	CH_3	CO_2Et	1.25 hr.	73 %	--	--	--	21	79	l
3	H	CN	5 min.	45 %	15	55	30	traces		m
4	H	CN	1 hr.	60 %		traces		94	6	m
5	H	CO_2Et	15 min.	22 %		traces		65	32	n

* Conditions: 100 mg of the mixture of 5 and 6 and 100 mg of 10 % Pd/C in a mixture of 8 ml of EtOAc and 8 ml of phosphate buffer pH 7 (c = 0.15 M) were hydrogenated at 1 bar H_2 over the period indicated in the table. After filtration the aqueous layer was concentrated and purified over a C-18 column.

However, the already unfavorable endocyclic/exocyclic ratio shifted even further towards the - presumably antibacterially inactive - exocyclic product. Attempted equilibration of the product of entry 3 (Table 2) in D_2O at room temperature over 3 hrs. had the adverse effect and led to a further increase in 8m. Short hydrogenolysis of ethoxycarbonylmethyl substituted carbapenem esters (5,6l and 5,6n) only gave a mixture of carbapenams 9 and 10[14]. Carbapenams were also produced upon prolonged hydrogenation of the 3-cyanomethyl carbapenem esters 5,6m.
None of the product mixtures of Table 2 showed interesting antibacterial activity.

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10. These were not the thermodynamic equilibria ratios. In most occasions the ratios changed over longer periods of time. Determined by NMR and HPLC.
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